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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,480	02/14/2008	Thomas A. Miller	21825P	4338

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EXAMINER	
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1625	

MAIL DATE	DELIVERY MODE
09/13/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,480	MILLER ET AL.	
	Examiner	Art Unit	
	Taylor Victor Oh	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,21,22,25,26,34 and 35* is/are pending in the application.

4a) Of the above claim(s) *26,34 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/07 & 8/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

The Status of Claims:

Claims 1-14,21-22, and 25-26, and 34-35 are pending.

Claims 1-14,21-22 are rejected.

Claims 25-26, and 34-35 are withdrawn from consideration.

DETAILED ACTION

1. Claims 1-14,21-22 are under consideration in this Office Action.

Priority

2. It is noted that this application is a 371 of PCT/US04/39221(11/23/04), which claims benefit of 60/525,333 (11/26/03).

Drawings

3. None.

Election/Restriction

Applicant's election with traverse of Group II (claims 1-14 and 21-22) on 8/05/10 is acknowledged.

Claims 1-14,21-22, and 25-26, and 34-35 (non-heterocyclic compounds or non-heteroaromatic compounds)are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected groups I and III, there being no allowable generic or linking claim.

Applicants argue in the followings:

a. The examiner has not identified prior art to define which technical features of the claimed invention makes over the prior art;

b. The division of Groups I and II is not a reasonable restriction since thecliemd invention also encompasses the possibility of R1 as heterocyclic or heteroaromatic, and R2 as a non-heterocyclic or non-heteroaromatic or vice-versa; thus, the rejoining Group I and II are requested.

In order to respond applicants' arguments fully, the examiner has decided to rewrite the restriction requirement in the followings:

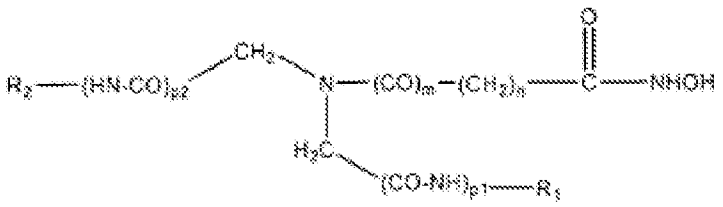
LACK OF UNITY

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claims 1-14,21-22, drawn to a non-heterocyclic or heteroaromatic compound of formula(I) and its pharmaceutical composition:



(I)

wherein

n is 2, 3, 4, 5, 6, 7 or 8;

m is 0 or 1;

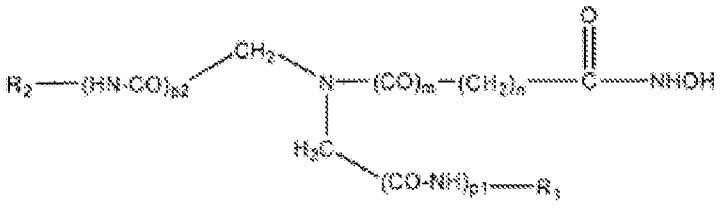
p_1 and p_2 are independently of each other 0 or 1;

R_1 and R_2 are independently of each other an unsubstituted or substituted aryl, cycloalkyl, , alkylaryl, alkylcycloalkyl or when at least one of p_1 or p_2 is not 0, R_1 or R_2 or both can also represent hydrogen or alkyl;

and pharmaceutically acceptable salts, solvates, hydrates, prodrugs and polymorphs thereof.

Group II has been further subdivided in the followings:

Group IIA, claims 1-14, 21-22 drawn to a heterocyclic compound or heteroaromatic compound of formula(I) and its pharmaceutical composition:



(I)

wherein

n is 2, 3, 4, 5, 6, 7 or 8;

m is 0 or 1;

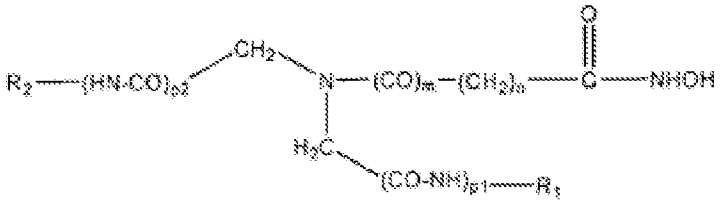
p_1 and p_2 are independently of each other 0 or 1;

R_1 and R_2 are independently of each other

, heteroaryl, , heterocyclyl, alkylheteroaryl, alkylheterocyclyl; or when p_1 and p_2 are both 0, R_1 and R_2 together with the $-CH_2-N-CH_2-$ group to which they are attached can also represent a nitrogen-containing heterocyclic ring;

and pharmaceutically acceptable salts, solvates, hydrates, prodrugs and polymorphs thereof.

Group IIB claims 1-14, 21-22 drawn to a heterocyclic compound or heteroaromatic compound of formula(I) and its pharmaceutical composition:



(I)

wherein

n is 2, 3, 4, 5, 6, 7 or 8;

m is 0 or 1;

p_1 and p_2 are independently of each other 0 or 1;

R_1 is , heteroaryl, , heterocyclyl, alkylheteroaryl, alkylheterocyclyl;

R_2 is an unsubstituted or substituted aryl, cycloalkyl, , alkylaryl, alkylcycloalkyl

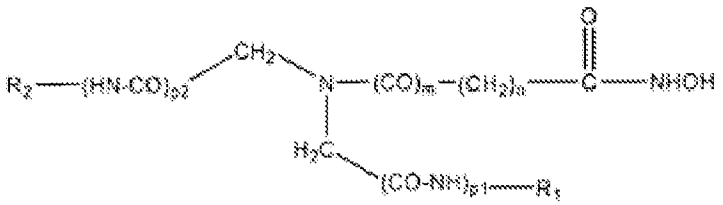
, heteroaryl, , heterocyclyl, alkylheteroaryl, alkylheterocyclyl;

or when at least one of p_1 or p_2 is not

0, R_1 or R_2 or both can also represent hydrogen or alkyl;

and pharmaceutically acceptable salts, solvates, hydrates, prodrugs and polymorphs thereof.

Group IIC claims 1-14, 21-22 drawn to a heterocyclic compound or heteroaromatic compound of formula(I) and its pharmaceutical composition:



(I)

wherein

n is 2, 3, 4, 5, 6, 7 or 8;

m is 0 or 1;

p_1 and p_2 are independently of each other 0 or 1;

R_2 is heteroaryl, heterocyclyl, alkylheteroaryl, alkylheterocyclyl;

R_1 is an unsubstituted or substituted aryl, cycloalkyl, alkylaryl, alkylcycloalkyl, heteroaryl, heterocyclyl, alkylheteroaryl, alkylheterocyclyl;

or when at least one of p_1 or p_2 is not 0, R_1 or R_2 or both can also represent hydrogen or alkyl;

and pharmaceutically acceptable salts, solvates, hydrates, prodrugs and polymorphs thereof.

Group III, claims 25-26 and 34-35, drawn to a method for treating cancer or tumor in a subject by administering the compound of the formula (I).

The inventions listed as Groups I, IIA,IIB, IIC, III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons.

The international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept (“ requirement of unity of invention ”).

PCT Rule 13.2 states “ Where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression “ special technical features” shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

In the instant case , the invention of Group I is directed to the non-heterocyclic or non-heteroaromatic compound of formula (I) and its pharmaceutical composition, whereas the invention of Group IIa is directed to the heterocyclic or heteroaromatic compound of formula (I) and its pharmaceutical composition. They have two distinct chemical structures and different functional groups attached to the back bone of formula(I) ;for example, to the heterocyclic compound of the invention of Group IIA, the various heterocyclic or heteroaromatic groups such as furanyl, thienyl, pyridyl , pyrrolyl,

pyrimidine, quinolinyl, morpholinyl or benzothiazolyl group and etc. are attached to the core structure; the presence of such different functional groups exhibits a chemically different activity during the reaction.

For example, the physical properties of those groups are specified below in the followings:

Furan
RN: 110-00-9

Physical Property	Value	Units
Melting Point	-8.56E+01	deg C
Boiling Point	31.5	deg C
log P (octanol-water)	1.34	(none)
Water Solubility	1.03E+04	mg/L
Vapor Pressure	500	mm Hg
Henry's Law Constant	5.40E-03	atm-m3/mole
Atmospheric OH Rate Constant	4.05E-11	cm3/molecule-sec

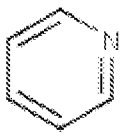
Thiophene
RN: 110-02-1

Physical Property	Value	Units
Melting Point	-3.94E+01	deg C
Boiling Point	84	deg C
log P (octanol-water)	1.81	(none)
Water Solubility	3010	mg/L
Vapor Pressure	79.7	mm Hg
Henry's Law Constant	2.92E-03	atm-m3/mole
Atmospheric OH Rate Constant	9.53E-12	cm3/molecule-sec

Pyrrole
RN: 109-97-7

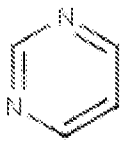
Physical Property	Value	Units
Melting Point	-2.34E+01	deg C
Boiling Point	129.7	deg C
pKa Dissociation Constant	17.6	(none)
log P (octanol-water)	0.75	(none)
Water Solubility	4.50E+04	mg/L
Vapor Pressure	8.36	mm Hg
Henry's Law Constant	1.80E-05	atm-m3/mole
Atmospheric OH Rate Constant	1.10E-13	cm3/molecule-sec

Pyridine
RN: 110-86-1



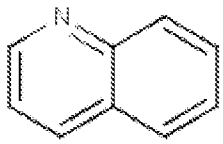
Physical Property	Value	Units
Melting Point	-4.16E+01	deg C
Boiling Point	115.2	deg C
pKa Dissociation Constant	5.229	(none)
log P (octanol-water)	0.65	(none)
Water Solubility	1.00E+06	mg/L
Vapor Pressure	20.8	mm Hg
Henry's Law Constant	1.10E-05	atm-m3/mole
Atmospheric OH Rate Constant	3.70E-13	cm3/molecule-sec

Pyrimidine
RN: 289-95-2



Physical Property	Value	Units
Melting Point	22	deg C
Boiling Point	123.8	deg C
pKa Dissociation Constant	1.23	(none)
log P (octanol-water)	-0.4	(none)
Water Solubility	1.00E+06	mg/L
Vapor Pressure	12.9	mm Hg
Henry's Law Constant	2.92E-06	atm-m3/mole
Atmospheric OH Rate Constant	2.30E-13	cm3/molecule-sec

Quinoline
RN: 91-22-5



Physical Property	Value	Units
Melting Point	-1.48E+01	deg C
Boiling Point	237.1	deg C
pKa Dissociation Constant	4.9	(none)
log P (octanol-water)	2.93	(none)
Water Solubility	6110	mg/L
Vapor Pressure	0.06	mm Hg
Henry's Law Constant	1.67E-08	atm-m3/mole
Atmospheric OH Rate Constant	1.16E-11	cm3/molecule-sec

When the melting point , the boiling point ,and the water solubility of each of the above groups are compared with one and another , the skilled artisan in the art would readily be noticeable that each group requires the unique reaction conditions for each reaction process to occur due to their wide variety of the physical properties. Because of those differences among them in any reaction process, they must have different modes of operation , different functions or different effects because each of their reactants has not only a completely different chemical structure with respect to the core structure, but also, each requires the unique reaction conditions for the reaction to take place.

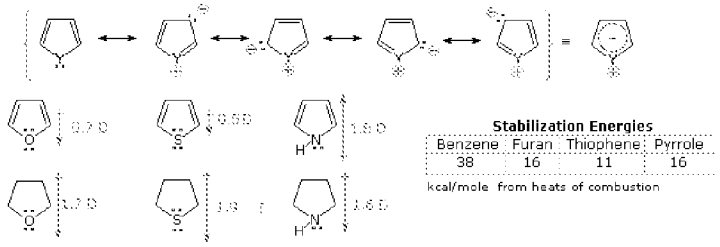
Furthermore, there is a comparison date regarding the difference of stabilization energies among benzene and heteroaromatic compounds, which can lead to the different reactivity during the reaction process as shown below:

Reactions

The chemical reactivity of the saturated members of this class of heterocycles: tetrahydrofuran, thiolane and pyrrolidine, resemble that of acyclic ethers, sulfides, and 2°-amines, and will not be described here. 1,3-Dioxolanes and dithiolanes are cyclic acetals and thioacetals. These units are commonly used as protective groups for aldehydes and ketones, and may be hydrolyzed by the action of aqueous acid.

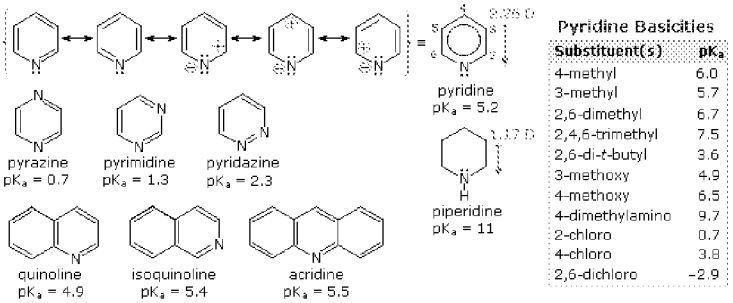
It is the "aromatic" unsaturated compounds, furan, thiophene and pyrrole that require our attention. In each case the heteroatom has at least one pair of non-bonding electrons that may combine with the four π-electrons of the double bonds to produce an annulene having an aromatic sextet of electrons. This is illustrated by the resonance description at the top of the following diagram. The heteroatom Y becomes sp^2-hybridized and aquires a positive charge as its electron pair is delocalized around the ring. An easily observed consequence of this delocalization is a change in dipole moment compared with the analogous saturated heterocycles, which all have strong dipoles with the heteroatom at the negative end. As expected, the aromatic heterocycles have much smaller dipole moments, or in the case of pyrrole a large dipole in the opposite direction. An important characteristic of aromaticity is enhanced thermodynamic stability, and this is usually demonstrated by relative heats of hydrogenation or heats of combustion measurements. By this standard, the three aromatic heterocycles under examination are stabilized, but to a lesser degree than benzene.

Additional evidence for the aromatic character of pyrrole is found in its exceptionally weak basicity (pK_a ca. 0) and strong acidity (pK_a = 15) for a 2°-amine. The corresponding values for the saturated amine pyrrolidine are: basicity 11.2 and acidity 32.



Regarding applicants 'argument about losing their identities of the individual compounds during the reaction process, this is not persuasive in view of evidence showing the remarkable pKa value difference among pyridine, pyrazine, pyrimidine, pyridazine, quinoline, isoquinoline, acridine, and etc below:

.



The diazines pyrazine, pyrimidine and pyridazine are all weaker bases than pyridine due to the inductive effect of the second nitrogen. However, the order of base strength is unexpected. A consideration of the polar contributors helps to explain the difference between pyrazine and pyrimidine, but the basicity of pyridazine seems anomalous. It has been suggested that electron pair repulsion involving the vicinal nitrogens destabilizes the neutral base relative to its conjugate acid.

All the above evidence do suggest that the presence of the different types of the heterocyclic or heteroaromatic moieties in the compounds can lead to the behavior of the compounds in a unpredictable way unlike applicants argument.

Thus, this becomes more prominent when the reactants containing heterocyclic or heteroaromatic groups in the compounds are compared with the ones with the non-hetero aromatic or cyclic groups in the compounds with respect to the reactivity or unexpected side effects during the course of the reaction process. Therefore, Group I and Group IIA are unrelated to each other. In addition, each invention has a different use and effect due to unrelated substituents attached to the core of the compounds. Therefore, there is no single general inventive concept and no unity of invention for the method or the process as defined in 37 CFR 1.475.

Similarly, as shown in the above, the same reasoning can be applied between Group I and Group IIB, Group I and Group IIC.

In the instant case, the invention of Group I is directed to the non-heterocyclic or non-heteroaromatic compound of formula (I) and its pharmaceutical composition, whereas the invention of Group III is directed to the method for treating cancer or tumor in a subject by administering the compound of the formula (I).

According to Ekwuribe et al (US 7,119,074), the reference discloses the method for the treatment of cancer or tumor by using a therapeutic compound conjugated to PEG-oligomer/polymer. From this, the Group III can be practiced without the requirement of the compound of the formula (I) from group I , which is the common link

between the Group III and the Group I. Therefore, the Group III is not required for the invention of Group I ; there is no special technical feature between Group III and Group I.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

The requirement is still deemed proper and is therefore made ***FINAL***.

Remarks:

The examiner recommends further applicants to elect the particular Group among Group IIA, Group IIB, Group IIC in the next communication.

The following Office Action is based on the election of the generic Group II.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14 and 21-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1, 6-9, and 12, the term "substituted " is recited. This expression is vague and indefinite because in the absence of the specific moieties intended to effectuate modification by the "substitution" or attachment to the chemical core claimed, the term "substituted" renders the claims in which it appears indefinite in all occurrences wherein applicants fails to articulate by chemical name, structural formula or sufficiently distinct functional language, the particular moieties applicants regards as those which will facilitate substitution, requisite to identifying the composition of matter claimed. Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 and 21-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making solvates and hydrates of the claimed compounds. The specification does not enable any person skilled in the art of synthetic organic chemistry to make the invention commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been

summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. In the present case the important factors leading to a conclusion of undue experimentation are the absence of any working example of a formed solvate, the lack of predictability in the art, and the broad scope of the claims.

c) There is no working example of any hydrate or solvate formed. The claims are drawn to solvates, yet the numerous examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

g) The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph

on page 358 of West (Solid State Chemistry). West, Anthony R., "Solid State Chemistry and its Applications, Wiley, New York, 1988, pages 358 & 365. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it is possible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate.

h) The breadth of the claims includes all of the hundreds of thousands of compounds of formulas (I)-(V) as well as the presently unknown list of solvents embraced by the term "solvate". Thus, the scope is broad.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is

clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Claims 1-14 and 21-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making prodrugs of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that

second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the prodrugs is found in page 20. c) There is no working example of a prodrug of a compound the formulas I-V. d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) Banker, G.S. et al, "Modern Pharmaceutics, 3ed.", Marcel Dekker, New York, 1996, pages 451 and 596. in the first sentence, third paragraph on page 596 states that “extensive development must be undertaken” to find a prodrug. f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that “the scope of enablement varies inversely with the degree of unpredictability of the factors involved",

and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formulas of claims 1 and 6-9, as well as the presently unknown list of potential prodrug derivatives embraced by claims 1 and 6-9.

MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to determine if any particular one is, in fact, a prodrug.

Claims 1-14 and 21-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In claims 1 and 6-9, the phrase" polymorphs " is recited. The specific PXRD pattern of a polymorphic Form is need to identify the specific crystalline Form uniquely different from the other polymorphic forms because the X- ray pattern of a pure crystalline substance can be considered as a "fingerprint" with each crystalline material having within limits, a unique diffraction pattern; furthermore, there are other characteristics to be used in order to distinguish each of the polymorphic Forms from the other polymorphic forms, such as bioavailability, solubility, dissolution rate, chemical and physical stability, melting point, color, filterability, density, and flow properties. In

addition, the polymorphs are further characterized by other analytical techniques such as differential scanning calorimetry, hot stage optical microscopy, and Raman and infrared spectroscopy. The above techniques are essential tools to be used for identifying each of the polymorphic Forms clearly; and it is up to applicants to select which critical parameters may be used so as to establish the unique polymorphic Forms. Since the above essential aspects are absent in the specification, the skilled artisan in the art is unable to determine which polymorphic forms of formulas I-V are suitable for the pharmaceutical composition with respect to the pharmaceutical bioavailability and the absence of the unique characteristic X-ray pattern for form X in the tablet and capsule form. Therefore, an appropriate correction is required.

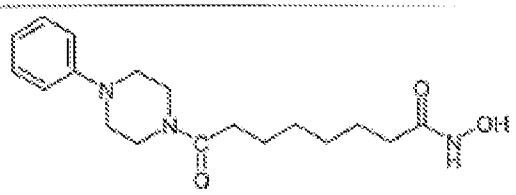
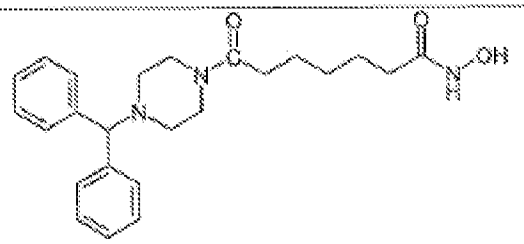
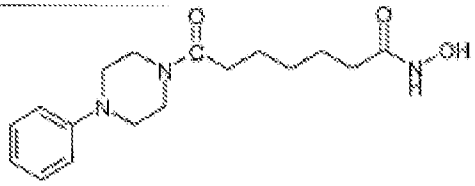
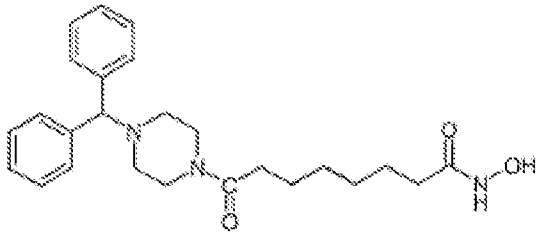
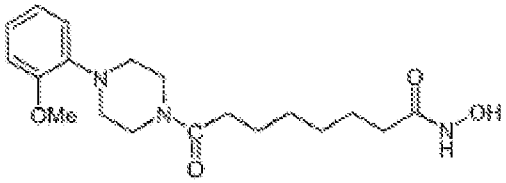
Claim Rejections - 35 USC § 102

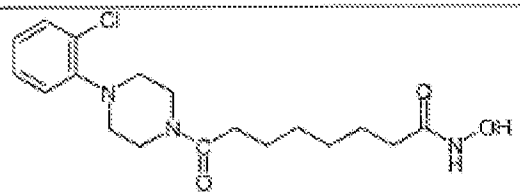
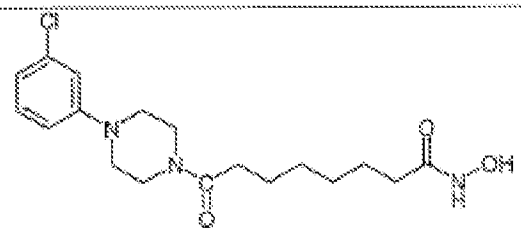
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

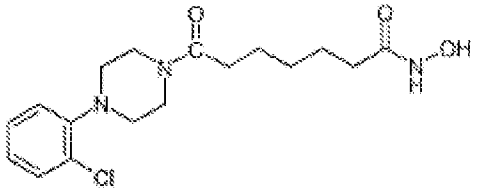
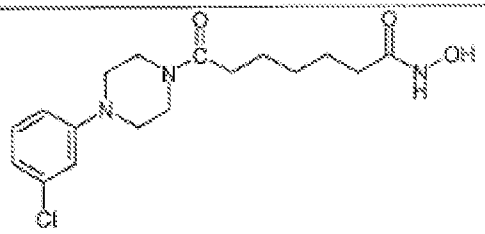
> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

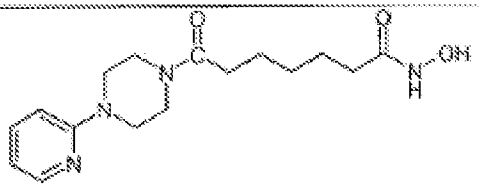
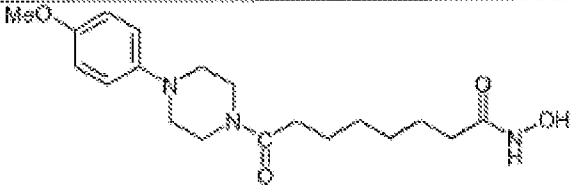
Claims 1-2,5 8,10-12, 14, and 21-22 are rejected under 35 U.S.C. 102(a) as being anticipated clearly by Watkins et al (WO 03/082288).

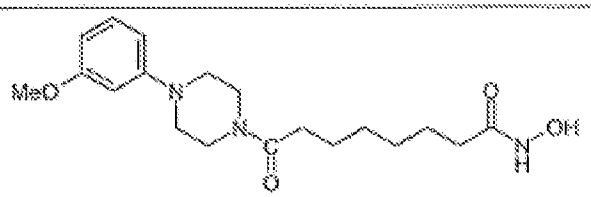
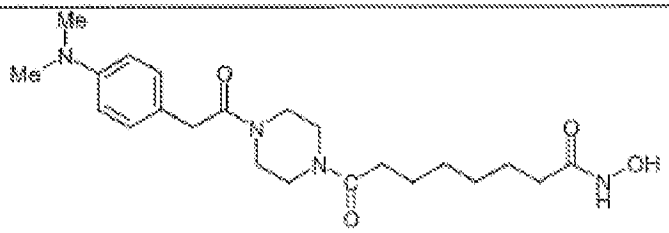
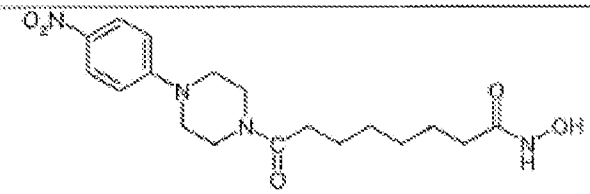
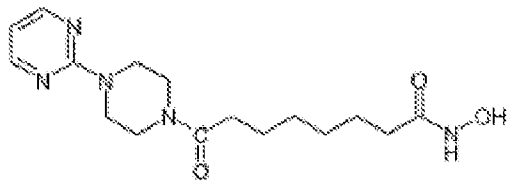
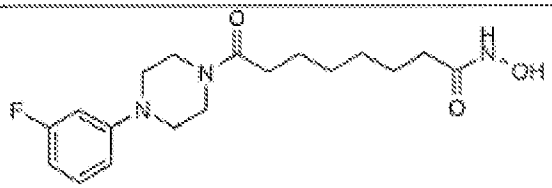
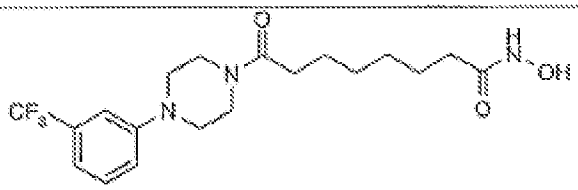
Watkins et al discloses the following compounds:

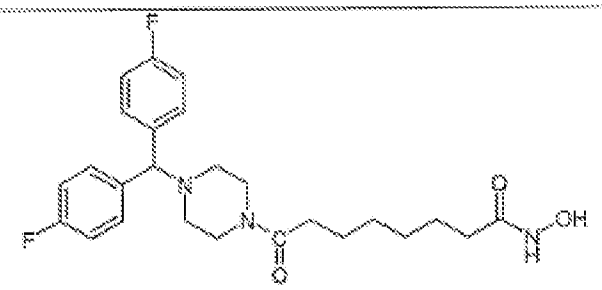
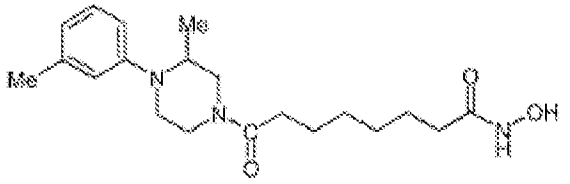
1.	
2.	
3.	
4.	
5.	

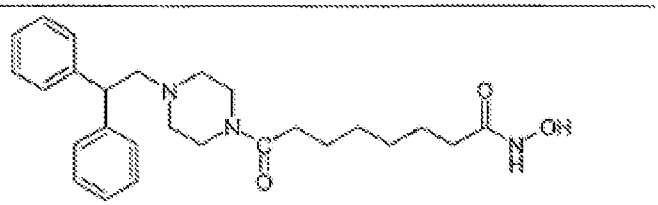
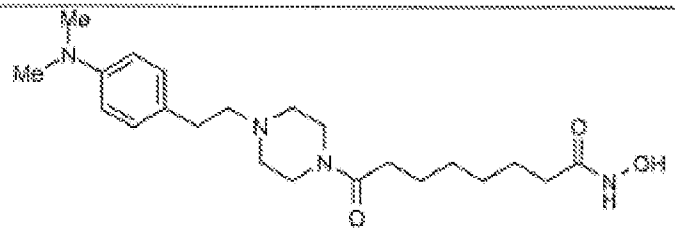
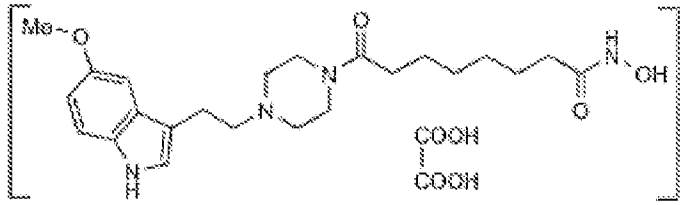
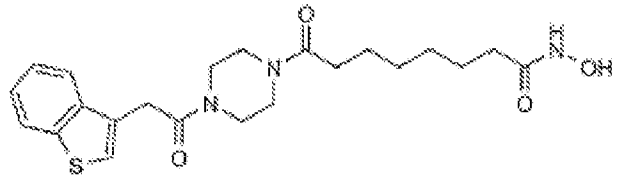
8.	
9.	

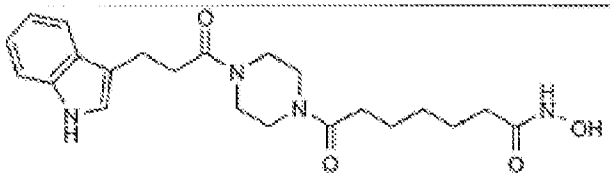
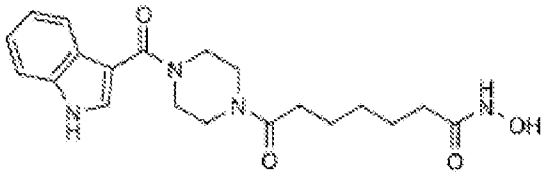
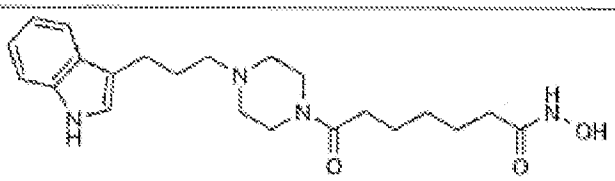
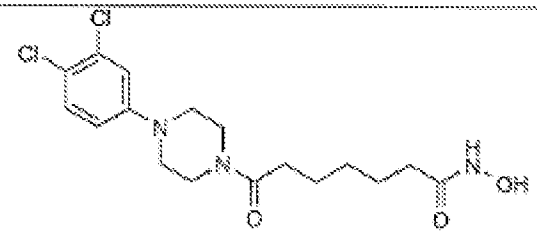
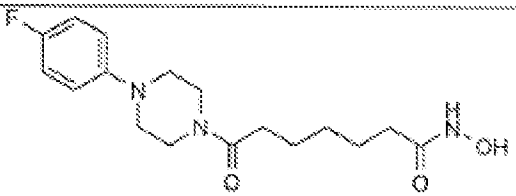
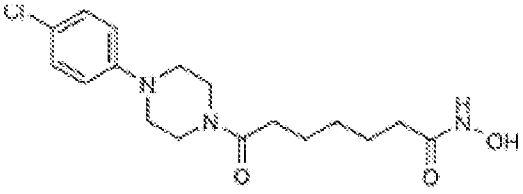
10.	
11.	

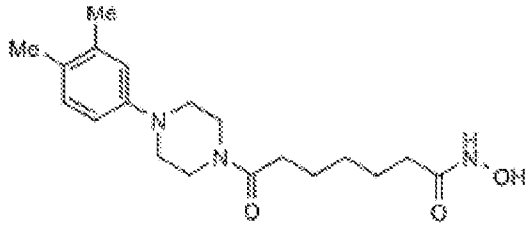
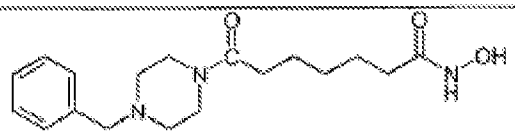
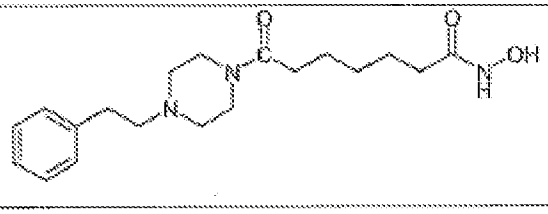
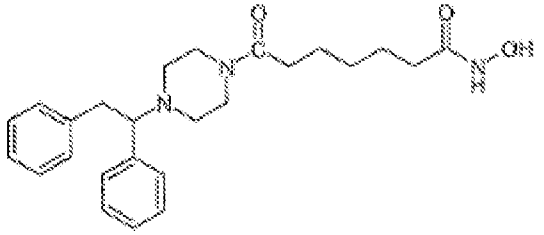
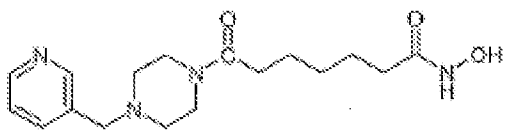
20.	
21.	

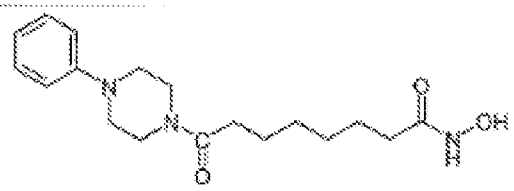
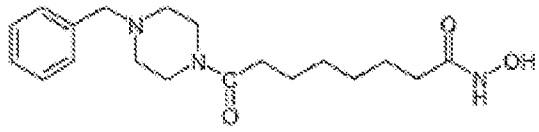
22.	
23.	
24.	
25.	
26.	
27.	

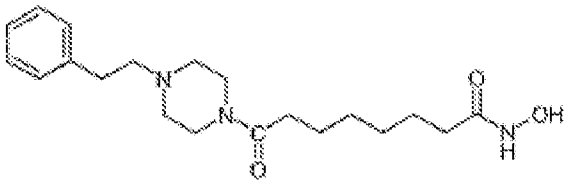
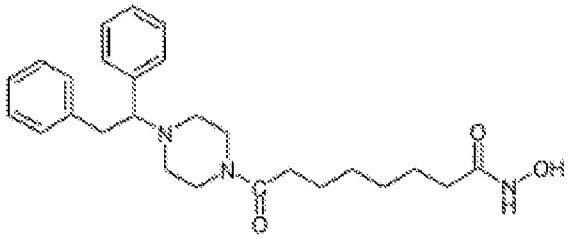
42.	
43.	

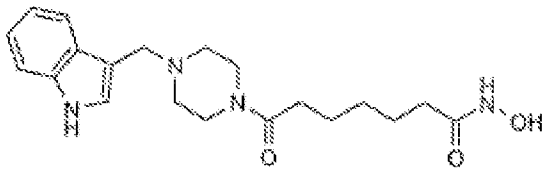
63.	
60.	
64.	
71.	

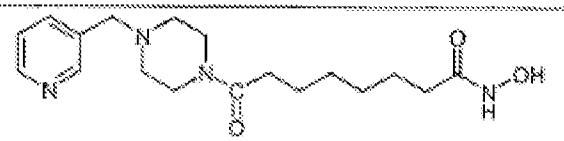
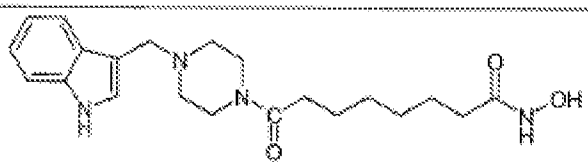
72.	
73.	
74.	
78.	
79.	
80.	

81.	
91.	
92.	
93.	
94.	

95.	
96.	

97.	
98.	



99.		
100.		

(see page 61-74).

These compounds are identical with the claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taylor Victor Oh whose telephone number is 571-272-0689. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Taylor Victor Oh, MSD,LAC
Primary Examiner
Art Unit :1625

/Taylor Victor Oh/
Primary Examiner, Art Unit 1625
9/08/10